Claims 1- 26 are in this case. Claims 2-4, 8-11, 15-17 and 21-24 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 1, 5-7, 12-14, 18-20, 25 and 26 have been rejected. Claims 1, 12, 14 and 25 have now been amended.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 1, 5-7, 12-14, 18-20, 25 and 26 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiners rejections are respectfully traversed. Claims 1, 12, 14 and 25 have now been amended.

With respect to claim 1 the Examiner points out that the term "modified LDL" is an unclear term, having no art recognized meaning, thus rendering claim 1 indefinite. Applicant wishes to point out that one skilled in the art would readily recognize the meaning of the phrase "modified LDL" since, as is evident from numerous prior art publications, (see, for example, US Pat No. 5,407,710 to Leonard; Pech MA, et al Ann Biol Clin (Paris) 1992;50:213-27; Mol MJ at al Neth J Med 1993;43:83-90; and Hoff HF and Hoppe G Curr Opin Lipidol 1995;6:317-25), this phrase is an accepted art term having a well defined meaning. Thus, it is the applicant's strong opinion that the term "modified LDL" recited in claims 1, 5, 14 and 18 is a well-defined art term having an art-recognized meaning, and as such, claims 1, 5, 14 and 18 are not rendered indefinite by the use of this phrase.

With respect to claims 7, 12, 20 and 25 the Examiner states that the phrase "active derivative", lacks antecedent basis thus rendering these claims indefinite. With respect to claims 7 and 20 the applicant wishes to point out that the limitation recited in these claims: "...wherein <u>said active component</u> is an active derivative of oxidized low density lipoprotein (Ox LDL)." derives

antecedent basis directly from the recitation of "an active component" in claims 1 and 14, respectively: "An immunological oral tolerance-inducing composition... comprising an active component selected from...".

With respect to claims 12 and 25, applicant has amended claims 12 and 25 to recite "...said active component..." in place of "...said active derivative...", to thereby correctly derive antecedent basis from claims 1 and 14, respectively, thus overcoming the Examiner's rejection in this case.

35 U.S.C. § 102(b) Rejections - Yesair

The Examiner has rejected claims 1, 5, 7, 12, 14, 18, 20 and 25 under 35 USC § 102(b) as being anticipated by Yesair (US Pat No 4,874,769). The Examiner's rejections are respectfully traversed. Claims 1 and 14 have now been amended.

The Examiner states that Yesair anticipates the pharmaceutical compositions and methods of the present invention since Yesair teaches a composition for oral administration containing LPC and other lipids, that LPC is a derivative of Ox LDL and a modified LDL and that Yesair teaches in vivo administration of said composition to the same population as taught by the present invention.

The present invention relates to a composition for inducing oral tolerance and to methods using such a composition for preventing or treating atherosclerosis. The composition of the present invention may comprise modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), beta$_2$-glycoprotein-1 (β_2-GP-1), functional derivatives thereof and mixtures thereof, in combination with a pharmaceutically acceptable carrier formulated for oral administration.

Induction of oral tolerance is based on the observations of the present inventors that oral administration of low doses of self antigens causes a

reduction of immune reactivity to these antigens. As demonstrated in the Examples section of the instant application, the present inventors have demonstrated, for the first time, a substantial reduction in atherosclerosis in LDL-RD mice using the compositions of the present invention (see page 18, Example 1).

Applicant would like to point out, that the compositions taught by Yesair would not be useful in reducing atherosclerosis in a subject, since these compositions are simply not formulated for the purpose of inducing immune tolerance to LPC.

Yesair teaches the inclusion of 1.0- 30% LPC in lipid micelles, in order to enhance the intestinal absorption of the fatty acids of the micelles into the lymphatic system (see column 7, lines 5-50). As such, the LPC is not an active component, formulated in a carrier, but is rather an integral component of the micelle vehicle, added to the lipid formula in order to facilitate the absorption of the other micelle components.

Since presentation of the tolerizing antigen at the gut associated lymphoid tissue depends on the exposure of relevant epitopes, it is highly unlikely that micelle formulations, which surround the active components with lipid vehicle components, would constitute an immunological oral tolerance-inducing composition. Indeed, micelles are generally not included in the methods of administration cited for induction of oral tolerance, but rather for enhanced systemic uptake of drugs and fat-soluble substances (see Shen H et al, Adv Drug Deliv Rev 2001; 50 Suppl 1: 5103-25, and Maurer N et al, Expert Opin Biol Ther 2001; 1: 923-47).

Thus, it is applicant's strong opinion that Yesair et al does not teach or infer the claimed compositions and methods for treating and/or preventing atherosclerosis of the present invention, therefore claims 1 and 14, and claims

dependent therefrom, are neither anticipated nor rendered obvious by the teachings of Yesair.

To further distinguish the present invention from Yesair, et al, and to expedite prosecution of this case, claim 1 is hereby amended to include the limitation "...the composition being formulated for inducing oral tolerance", thereby limiting the invention to compositions being capable of stimulating an immune response which leads to tolerance, support for such an amendment is provided throughout the instant application, see for example "**LDL isolation, oxidation and characterization**" in the **Materials and Methods** section of the instant application (page 15, last paragraph), in which the process of ultracentrifugation, dialysis against EDTA, filtration and oxidation of LDL with copper sulfate, and subsequent confirmation of extent of oxidation, is detailed. Further care is taken to distinguish Ox LDL active in inducing oral tolerance from non oral tolerance-inducing LDL when measuring anti-Ox LDL antibody titers, a crucial method of evaluating induction of tolerance ("**Determination of anti-Ox LDL antibody titers**", in the **Materials and Methods** section of the instant application; page 16, third paragraph): "The titer of anti-Ox LDL antibodies is calculated by subtracting the value obtained from binding to native LDL from the binding to Ox LDL". In addition, claim 14 is hereby amended to include the limitation "...thereby inhibiting at least one atherosclerosis-related symptom in said subject", thus limiting the method of the present invention to the administration of compositions possessing the ability to induce oral tolerance to atherosclerosis in a manner which enables inhibition/prevention of atherosclerosis-related symptoms in a subject.

35 U.S.C. § 102(e) Rejections - Witztum et al (US Pat No 6,225,070).

The Examiner has rejected claims 1, 5- 7, 12 and 13 under 35 USC § 102(e) as being anticipated by Witztum et al. The Examiner's rejections are respectfully traversed. Claims 1 and 12 have now been amended.

The Examiner states that Witztum teaches a composition containing MDA-LPL or Acetyl-LDL in PBS which anticipate the compositions of the present invention.

Contrary to the Examiner's assertion, Witztum et al do not describe compositions or the use thereof for treatment and/or prevention of atherosclerosis. Although Witztum et al teaches various methods for preparation of "...Artifactual Oxidation Protected Oxidized Lipoprotein Antigens", using freshly prepared LDL and HLDL (column 18), they do not describe, nor do they suggest the formulation of these oxidized lipoprotein antigens in compounds intended for administration to a subject in need of treatment, but rather teach their use as antigens for "...screening of plasma, hybridoma supernatants, ascites and purified antibodies...". The explicitly stated intent of the invention of Witztum et al is to "...provide monoclonal antibodies for in vivo and in vitro use..."(column 3, line 59-60).

Indeed, Witztum et al describe and claim methods of detection, measurement and monitoring the presence and formation of oxidation-specific epitopes on oxidized blood lipoproteins. Witztum et al. do not teach active immunization of a subject or animals with the modified LDL antigens, or the preparation of any antibodies for immune therapy. The methods taught relate to the identification of anti-oxidized LDL epitopes with the oxidized LDL preparations described.

Since compositions commonly used for immunological screening are substantially different from those used in the treatment and/or prevention of disease, the immunological screening being performed in-vitro, formulated to conform to the biochemical parameters of the cell-culture environment, and

the antigenicity of "self" molecules cannot be easily deduced (Ogra et al Clin Microbiol Rev 2001; 14: 430-45 and Chen et al J Control Release 2000; 67:117-28), one of ordinary skill in the art would not be motivated to prepare or administer the antigens described by Witztum et al. in order to induce immune tolerance in an animal or subject.

Furthermore, the applicant has claimed the use of oxidized LDL to modify, in a selective manner, a pathogenic immune response being causally involved in the initiation and progress of atherosclerosis. In sharp contrast, Witztum et al claim the use of mAbs to oxidized LDL to alter the process of LDL oxidation, or the susceptibility of LDL to oxidation, i.e. as an antioxidant. Thus, it is the applicant's strong opinion that Witztum et al cannot be interpreted as anticipating or rendering obvious the composition or methods claimed in claims 1, 5- 7, 12 and 13 of the present invention.

35 U.S.C. § 103(a) Rejections - Strober et al, in view of Hansson et al, Resch et al and Sima et al.

The Examiner has rejected claims 1, 5- 7, 12, 14, 18-20, 25 and 26 under 35 USC § 103(a) as being unpatentable over Strober et al in view of Hansson et al, Resch et al and Sima et al. The Examiner's rejections are respectfully traversed. Claims 1, 12, 14 and 25 have now been amended.

The Examiner states that Strober teach compositions of autoimmune antigens and the use of said compositions to treat autoimmune disease and that this method can be used to treat autoimmune disease mediated by T cells and B cells. The Examiner further states that Hansson et al and Sima et al teach that Ox-LDL functions as an autoantigen in atherosclerosis and that Resch et al teaches that autoantibodies bind modified/derivatives of LDL, and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the

time of the invention to have created the claimed invention.

Applicant is of the opinion that Strober et al do not teach nor provide motivation for the use of the antigens recited in the claims to treat atherosclerosis.

Strober et al teaches "... a method for enhancing oral tolerance to an antigen associated with an autoimmune disease ... comprising orally administering to the subject an antigen associated with the autoimmune disease ... and administering an inhibitor of IL-12 in amounts sufficient to enhance oral tolerance" (page 4, line 4-9). As is clearly stated in the specification of Intn'l. Pat. No. WO98/16248the invention taught by Strober et al is intended for enhancement, and not induction of oral tolerance, by the suppression of IL-12 via anti-IL-12 antibodies, p40 IL-12 homodimers, inhibitors of IL-12 production, etc. (page 6, line 23-29).

Strober et al. do not describe nor do they suggest compositions suitable for treating atherosclerosis, let alone describe or suggest methodology for treating and/or preventing atherosclerosis.

Furthermore, Strober et al teach the use of a method for enhancement of oral tolerance to autoimmune diseases, many of which are specified in the claims and detailed description, and "any other autoimmune disease now known or discovered in the future". Nowhere is atherosclerosis in this recitation of autoimmune diseases, and this is not to be regarded as an oversight. Atherosclerosis, and its related conditions, can by no means be considered an autoimmune disease.

Indeed, prior art teaches away from the inclusion of atherosclerosis as an autoimmune disease. Autoimmune diseases or conditions are defined as those in which an immune response (humoral or cellular) possess pathogenic properties that should be either identified in an autoimmune state or be

transferable to non-immune animals (Harrison's Textbook of Internal Medicine, Autoimmune Diseases). Atherosclerosis is primarily a disease of deranged lipid metabolism, whose treatment is directed towards intervention in the metabolic processes, i.e. statins, etc. As such, Strober et al provides no motivation for the application of compositions for or methods of oral tolerance to the treatment and/or prevention of atherosclerosis.

Moreover, atherosclerosis progresses gradually and does not have the classic flare and remission of autoimmune disease. Indeed, unlike all autoimmune diseases, atherosclerosis does not respond to corticosteroids or immune suppressants: treatment with cyclosporin A further aggravates the disease (Emeson et al Am J Pathol 1993;142: 1906-15). In fact, Meir et al, in a recent review of the contribution of inflammation to atherosclerosis in humans (Commentaries, Int. Atheroscler Soc.) concluded that "thus far there is neither cogent clinical evidence that anti-inflammatory agents decrease vascular morbidity or mortality, nor cogent evidence linking them to decreased atherogenesis in humans. Inflammation may simply be a marker of active disease".

These distinctive features of atherosclerosis would prevent an ordinary skilled artisan from applying the teachings of Strober et al to treating atherosclerosis since atherosclerosis would not be recognized by one of ordinary skill in the art as an autoimmune disease.

Although Hansson et al, Resch et al and Sima et al all teach the presence of anti-oxidized LDL antibodies in atherosclerosis, the role of this immune response in the pathogenesis and treatment of the disease remains unclear (see, for example, Meir, at al, above), and one ordinarily skilled in the art would not be motivated to use modified LDL and other antigens recited in the present invention for treatment and/or prevention of atherosclerosis especially via oral induction of immune tolerance.

This is particularly true when considering that immunization with classic autoantigens leads to induction of autoimmune disease in animal models, such as collagen in RA (reviewed by Williams RO Clin Exp Immunol 1998; 114:330) and myelin basic protein in rat model of multiple sclerosis (Fujinam et al J Exp Med 1978;148:1716). In contrast, immunization with oxidized LDL causes a reduction in the severity of atherosclerosis (Palinski et al PNAS 1995;92:821-25; George et al Atherosclerosis 1998;138:147-52; Freigang et al Arterioscler Thromb Vasc Biol 1998;18:1972-82 and Zhou et al Arterioscler Thromb Vasc Biol 2001;21:108-114).

In addition, neither Sima et al, Resch et al nor Hansson et al make any reference to oral tolerance, despite the wide recognition of oral tolerance techniques. The novelty of the methods of the present invention is further emphasized, considering that Resch et al, merely states that the demonstration of anti-oxidized LDL antibodies "...can be used as an indicator of the extent of atherosclerosis...". Sima et al likewise failed to suggest any therapeutic potential of the "...immunoactive components (modified lipoproteins) in the atherosclerotic process." Similarly, Hansson et al, unable to conclude whether the local immune response in plaque is "...an aggravating factor...or protective...", and thus fails to recognize any potential for protective induction of tolerance to oxidized LDL. Similar omission of therapeutic potential can be found in the report of Wick and Xu from the same citation as the abovementioned authors.

While techniques of inducing oral tolerance are well known in the art for many years, the parameters useful for inducing effective oral tolerance cannot be deduced from antigenic activity in conventional immunization, and must result from extensive empirical experimentation. Thus, one ordinarily skilled in the art would not have expected to prepare such compositions or

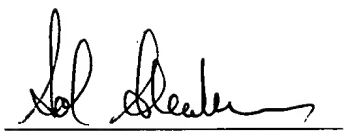
develop the methods of the present invention with a reasonable degree of success without having to resort to undue trial and error experimentation.

Indeed, many studies have demonstrated the complexities inherent in manipulating the "balance between reacting and non-reacting" in the immune system (for recent reviews of problems in oral and mucosal tolerance, see Ogra et al Clin Microbiol Rev 2001;14:430-45; Chen et al J Control Release 2000;67:117-28; and Lehner et al J Infect Dis 1999; 179 Suppl 3:S489-92). Furthermore, oral feeding is a particularly unpredictable route of administration, due to digestive and metabolic influences on the antigens. Thus, the existence of anti-oxidized LDL antibodies in atherosclerosis does not make prima facie obvious the usefulness of oxidized LDL for inducing oral tolerance.

Since the immune response to oxidized LDL is not that which would be expected for a classic autoimmune antigen, and since the prior art cited herein fails to teach or even suggest treatment of atherosclerosis via oral induction of immune tolerance, it is Applicant's strong opinion that the immunological oral tolerance inducing compositions and methods for their use in treating and preventing atherosclerosis of the present invention are patentable over Strober in view of Hansson et al, Resch et al and Sima et al.

In view of the above amendments and remarks it is respectfully submitted that claims 1, 5-7, 12-14, 18-20, 25 and 26 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



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Date: February 10, 2002.
Enc.
Version with marking to show changes made
A two month extension fee

VERSION WITH MARKING TO SHOW CHANGES MADE

In the Claims:

1. (Amended) An immunological oral tolerance-inducing composition for prevention and/or treatment of atherosclerosis, comprising an active component selected from the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), beta$_2$-glycoprotein-1 (beta$_2$GP-1), functional derivatives thereof and mixtures thereof, in combination with a pharmaceutically acceptable carrier for oral administration, the composition being formulated for inducing oral tolerance.

12. (Amended) An immunological tolerance-inducing composition according to claim 1, wherein said active component~~derivative~~ is lysophosphatidyl choline (LPC).

14. (Amended) A method for prevention and/or treatment of atherosclerosis in a subject, comprising administering an immunological oral tolerance-inducing composition comprising an active component selected from the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), beta$_2$-glycoprotein-1 (beta$_2$GP-1), functional derivatives thereof and mixtures thereof, in combination with a pharmaceutically acceptable carrier for oral administration, thereby inhibiting at least one atherosclerosis-related symptom in said subject.

25. (Amended) A method according to claim 14, wherein said active ~~derivative~~ component is lysophosphatidyl choline (LPC).

ABSTRACT:

An immunological oral tolerance-inducing composition for prevention and/or treatment of atherosclerosis, comprising an active component selected from the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), $beta_2$-glycoprotein-1 ($beta_2$GP-1), functional derivatives thereof and mixtures thereof, in combination with a pharmaceutically acceptable carrier for oral administration, the composition being formulated for inducing oral tolerance.